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2008 Thomas Parran Award Lecture: Translational Research, STD Control, and Health Disparities

A Challenge and an Opportunity

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THE UNITED STATES CAN do a better job of sexually transmitted disease (STD) control. The question is how to do it. In recent years, United States STD rates have been flat or have increased.[1] National syphilis rates have once again begun to climb; since 2000, in addition to continued increased rates amongst men who have sex with men, more recently infections have also increased among heterosexual minority populations living in the southeastern United States. Gonorrhea rates have been relatively flat for over a decade. In 2006, reported rates of *Chlamydia trachomatis* infection exceeded 1,000,000 cases for the first time in history, representing the first time rates of a reportable STD in the United States had surpassed the 1 million case mark since the mid-1970s. It is now time to consider how to revitalize STD control efforts, celebrating progress over recent years and following on with consideration of how to "do better." This presentation provides a bully pulpit for me to present 1 person's thoughts on how that might be accomplished.

In considering STDs and STD control, clinicians have often framed their thought processes using Anderson and May's reproductive rate equation[2] in which the reproductive rate of an infection is determined multiplicatively by the combinations of factors contributing to the 3 major elements of the equation–infectivity, sexual partner selection, and the duration of infectivity. Importantly, however, this equation represents an equilibrium relationship in which change to any of the 3 equation components will lead to change in the reproductive rate within the population, leading toward a new equilibrium. Should STD infectivity, sexual partner selection, and the duration of infectivity all remain stable, the tendency is then for rates to plateau. Thus, to accomplish further progress in the US STD control efforts at this time, it would seem that once again changes to 1 or more of the components of the reproductive rate equation are needed. The hypothesis I wish to promote in this presentation is that using the concept of translational research to reframe measurement of STD control efforts can contribute in important ways to improving STD control. I also suggest that the need for concerted efforts, including resource allocation (or reallocation), are needed to address existing health disparities and STD-associated stigma to fully realize the opportunities presented through translational research as applied to STD control.

Over the past few years, translational research has been emphasized through large investments by the U.S. National Institutes of Health as well as in numerous publications in a variety of different settings.[3] The term "translational research," although widely used, means different things to different people. Irrespective of the definition however, for most the term refers to the concept of research conducted in such a way that the movement of research findings into more generalized clinical practice is accelerated. For many the term translational research suggests the "bench to bedside" application of new basic science research findings to influence clinical practice through development of new diagnostics or therapeutics. Although this is certainly part of the translational research paradigm, an alternate and broader approach to the topic is possible by subdividing translational research into "T1" and "T2" research.[3] In this broader view, T1 research is defined as carrying out the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans. In contrast, T2 research represents research evaluating the translation of clinical research findings into everyday clinical practice and health decision making, i.e., the transformation of experimentally demonstrated efficacy into broader, population-based efficacy. Both effective T1 and T2 research are required to truly improve health care outcomes.

Recently T1 research has provided a number of exciting new tools for STD prevention and management. These include development of nucleic acid amplification tests (NAATs) for diagnosis of common bacterial and viral STDs,[4,5] development of highly effective vaccines for the prevention of human papillomavirus infection,[6] the availability of type-specific tests for serologic diagnosis of herpes simplex virus, demonstration that chronic suppressive antiviral therapy will prevent herpes simplex virus transmission to uninfected partners,[7] randomized clinical trials demonstrating that partner delivered therapy is a useful mechanism for getting therapy to sexual partners exposed to infected partners,[8] and studies showing that circumcision of uncircumcised men can effectively reduce the risk of HIV acquisition.[9,10]

One familiar example of both the potential and the initial trans-

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lation of that potential into population-based efficacy for STD control is the large body of research carried out over the past decade exploring the utility of NAATs for detection of gonococcal and chlamydial infection, as well as the routine adoption of these improved tools for gonorrhea and chlamydial diagnosis.[4,5,11–14] NAATs provide clinicians with powerful new tools for STD diagnosis, being substantially more sensitive for diagnosis of both chlamydial and gonococcal infections than previously available tests. Equally and perhaps more important for T2 research, they allow simpler and more-forgiving specimen collection than the previously available diagnostic tests for which specimen quality was an important determinant of test performance. As a result, in addition to the benefits of testing with more sensitive tests for STD diagnosis compared to using classic endocervical and urethral swab specimens for STD diagnosis, the NAATs now allow accurate diagnosis of gonococcal and chlamydial infection using initial voided urine and, for women, vaginal swabs obtained either by patients themselves or their clinicians.[4,5,11–14] These simpler, more-forgiving specimen types in turn provide the as yet not fully realized opportunity to use NAATs to expand testing to settings where testing has not been previously offered to reach new populations and further enhance efforts for STD control. Numerous studies have now demonstrated the efficacy of these tests for identifying substantial STD rates in a variety of nonhealthcare settings including school-based clinics,[15] in detention centers and jails,[16–18] for diagnosis of infections in military recruits, for testing homeless persons through street outreach or for other hard to reach populations such as persons receiving treatment for substance abuse.[19–26] In each of these settings, simplified specimen collection testing has removed an important disincentive to testing–the inconvenience and discomfort of specimen collection–from the application of efforts to diagnose STDs in these populations. Effective, realistic, and programmatic increase of these activities has the potential to increase the effectiveness of STD control, may have contributed to increased chlamydial diagnoses in recent years and seems to be in the process of translation from research into routine practice.

Measurement of benefits derived through NAATs testing may also suggest opportunities for T2 research and programmatic evolution of STD control efforts. As STD testing is offered to difficult-to-reach populations, change in the metrics used to gauge the success of such programs may also be useful. To date, the benefits of improved diagnostic testing have been largely described using classic measures of STD morbidity such as numbers of infections diagnosed. As we begin to use translational research paradigms it is appropriate to consider different outcome measures to evaluate the utility of new strategies for STD control. Specifically, for NAATs I would suggest that for evaluating the success of STD control measures, the outcome of interest is no longer the number of infections diagnosed but should evolve to include parameters that measure infection treatment such as the proportion of cases treated and the time interval between testing and treatment. Just as for the HPV vaccine in which the outcome of interest is not vaccine doses administered but is abnormal pap smears, cancers, and procedures averted through vaccine use, the success of control efforts for other STDs should adopt other, processed-based outcome measures such as persons treated, time to treatment and, if possible, changes in the incidence of STD sequelae as potentially better measures of the success of STD control efforts.

Consideration of process-based outcome measures may provide other opportunities for improved STD control through application of the products of T2 continuous quality improvement research to day-to-day STD care. An example of such operational research directed at evaluating the provision of care is found with several observations made while working with colleagues first in Baltimore, MD and more recently in Birmingham, AL.[27,28] This story began with a Baltimore study to compare the utility of chlamydial point of care diagnostic tests to standard cell culture for chlamydial diagnosis.[27] The operative hypothesis in this study was that, because of the issues related to delay of therapy and loss to follow-up of women who had positive laboratory-based screening tests for *C. trachomatis* infection, the somewhat lower sensitivity of the point of care tests for chlamydial diagnosis would be more than offset by the fact that virtually all women identified using point of care tests could be more expeditiously treated at the time of initial evaluation.[29] Because of the suboptimal performance of the point of care test utilized, the study did not demonstrate increased treatment of persons with chlamydial infection; however, it did identify important opportunities to improve care for patients with positive chlamydia screening tests. Of women in the study with positive laboratory-based (culture) screening tests for *C. trachomatis*, no subsequent follow-up or treatment could be documented in 26% and, of women treated, only 81% were documented to receive treatment within 30 days of diagnosis. Our research has since documented similar proportions of women not receiving timely treatment among patients seen at our Birmingham STD Clinic and through testing performed in the context of provision of care in emergency rooms.[28,30] Furthermore, in our studies we have found that 2% to 5% of patients treated following positive laboratory-based screening tests, will go on to develop complications (pelvic inflammatory disease, epididymitis) in the interval between initial screening and receipt of treatment for infections diagnosed through screening.[27,30,31] Taken together, these data suggest that the proportion of persons with positive tests treated and time to treatment might provide readily measured data on the success of our STD control efforts as well as potentially point to useful opportunities to improve the process of delivering care. This has been the case at the Department of Health STD Clinics, Jefferson County, AL where we have recently adopted a measure of the proportion of patients treated as a routinely measured clinic performance variable and have reduced the proportions of patients who were untreated at 30 days following testing for their infections from over 20% of positive tests to 4%. (Elizabeth Turnipseed, MD, MPH–personal communication).

In addition to conscious application of translational research paradigms to STD control efforts and application of T2 research observations to continuous quality improvement-type efforts to improve care for persons with and at risk for STDs, I would also suggest that another great step toward improved STD control for the US would be for formal, forthright acknowledgement of the fact that STDs remain a prominent example of US health disparities. To address these disparities, there is a need to consider both reallocation of resources to programs serving populations with the greatest STD morbidity as well as measures to address STD-related stigma[32] through a shift in the philosophical underpinnings of STD control efforts. A superb example of the extent to which STDs remain unevenly distributed within American society is found in a recent paper by Hallfors et al.[33] who used the population-based data available through the Wave III of the national Longitudinal Study of Adolescent Health (Add Health) study to demonstrate that the prevalence of treatable STDs such as gonorrhea, chlamydial infection, and trichomoniasis were more than 6 times more common among blacks than whites, even following adjustment for potential modifiers such as marital status, educational attainment, income, partner number, and drug and alcohol use. Data such as these serve to emphasize that profound disparities in STD prevalence remain throughout the United States and

would seem to justify reallocation of Federal and local STD prevention and control funds to address these disparities, spending proportionately more funds to reduce morbidity in the population who are most affected.

The origins of the health disparities mentioned above are multiple and longstanding. I would suggest that for efforts to control STDs for all populations, 1 contributing element which must be addressed is the pervasive issue of stigmatization of persons with and at risk for STD.[32] That stigma is pervasive and needs to be addressed has been recognized and reiterated since Thomas Parran wrote Shadow on the Land in 1937[34] but sadly little has been done about it. A recent analysis of the provision of care for Americans receiving health care through health maintenance organizations (HMOs) provided a striking example of how stigma-based preconceptions may impact provision of routine medical care. Landon et al.[35] compared the achievement of 11 health plan employer data and information set (HEDIS)-defined benchmarks for healthcare among persons receiving care in commercial only, mixed commercial-Medicaid, and Medicaid only HMOs. The measures evaluated included widely accepted benchmarks such as hemoglobin A1C measurement in diabetes patients, breast cancer screening, successful hypertension control, adolescent vaccination rates, and chlamydial screening rates among the 11 HEDIS benchmarks studied. Although the article showed that, compared with patients receiving care through Medicaid-funded HMOs, patients who received their care from commercial HMOs had higher levels of benchmark attainment across the board, there was 1 glaring exception. The single variable in which this tendency was reversed was in screening for *C. trachomatis*. Commercial only HMOs achieved chlamydia screening benchmarks 23.7% of the time, whereas the Medicaid funded HMOs which provided care for a predominantly lower socioeconomic class, minority population, achieved or exceeded the screening benchmark 40% of the time. This difference in chlamydial screening, in a direction opposite to all other HEDIS benchmarks studied can be interpreted as yet a possible indicator of assumptions by health care providers that STDs are disproportionately expected to occur and are sought in minority populations despite ample evidence that chlamydial infections are common throughout all populations of young women. To address such assumptions and all of the other stigma-driven factors that conspire to hamper US STD control efforts, we need to find a better way to promote STD management. I would suggest that 1 way to do so is through abandonment of our current disease-based STD management orientation and incorporation of STD management as a central element of increased emphasis on sexual health as an essential human right.

It is my belief that transition from a disease focused orientation for STD control efforts to a sexual health-based perspective would ultimately lead to improved STD control through both permissive encouragement of improved health care seeking by persons at risk for STI, through improved diagnosis of STD by clinicians and through enhanced STD screening as the stigma surrounding STDs dissipates. The foundation of this belief is one which was set forth as it related to HIV control efforts by Dr. Jonathan Mann before his untimely death in 1998, that sexual health, as it related to viewing all aspects of human sexual interaction is a basic human right. Thus, persons should not have to enter into sexual relationships with a fear that to do so might lead to untoward effects such as transmission of infection to a loved one (including children born to infected mothers), disease and life-course altering disease complications and sequelae (infertility, ectopic pregnancy, malignancy, AIDS, etc), or with fear of judgment by others as somehow being unclean and socially unacceptable. Studies showing the remarkably widespread prevalence of viral STDs such as human papillomavirus or herpes simplex infections, or that 1 in 4 US adolescents can be expected to have an STI clearly demonstrate that STDs are widespread throughout the population and not "someone else's" problem. Further, the long intervals that often separate STD incidence, which tends to occur early in a person's sexual life-course from a diagnosis of the consequences of these infections (Acquired Immunodeficiency Syndrome, cervical cancer, infertility are among the obvious examples) further serve to remind us that promotion of sexual health will not only serve the nation's health needs but will also help to prevent disproportionate penalization of persons who have made youthful errors in judgment as they relate to STD risk far later in their lives. A national campaign based on sexual health rather than one focused on disease would allow for institution of educational programs incorporating sexual health as 1 element of health promotion.

STD clinicians and thought leaders within the field of STD could also do much to begin to shift consideration of their efforts from disease-related to health promoting considerations. For instance, by measuring STDs treated rather than diagnosed, they would be in a position to celebrate having taken steps to prevent possible unintended transmission to others, to state that the treatment may have also reduced their clients' risk for complications and the consequences of STD. Such an approach would also make it easier to encourage persons with STIs to extend the benefits of diagnosis and treatment to their sexual partners, thereby addressing another important element of STI control efforts. To do so would be a useful, readily accomplished step toward making the job of STD control more effective and more easily accepted.

The changes suggested above would not come simply, but in my opinion, might contribute ultimately to lasting improvement in STD control, a widely shared goal by all participants in STD management efforts at all levels.

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